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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,621	04/11/2001	Judy Raucy	PUR-00114.P.1.1	1829

24232 7590 06/03/2003

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EXAMINER	
SHEINBERG, MONIKA B	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,621	RAUCY, JUDY	
	Examiner	Art Unit	
	Monika B Sheinberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Supplemental action* .

SUPPLEMENTAL ACTION

Response to Amendment C and Phone Interview

Applicants' attorney, David Preston, was notified on 28 March 2003 of the supplemental action necessitated by an additional rejection and that the period for reply will restart from the mailing of this supplemental action. The issues discussed during the phone interview held on 25 March 2003, are incorporated into the instant supplemental action. The previous office action mailed 1February 2003, are referred to herein. This action contains an additional rejections under 35 U.S.C. § 101, 112 (first and second paragraph), 102(Honkakoski et al.), and 103 (Honkakoski et al., Iyer et al., Windmill et al.) which were absent from the previous office action.

Applicants' arguments, filed 21 October 2002, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. Claims 21-83 have been examined herein.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 21-51 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, nonstatutory subject matter. The instant claims encompass naturally occurring, human and nonhuman multicellular living organisms, including animals that are not patentable subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-83 are rejected under 35 U.S.C. 112, **first** paragraph, because the specification, while being enabling for the following isolated and/or cultured cells, does not reasonably provide enablement for any cell (in vivo, or in vitro). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to perform the invention commensurate in scope with these claims. Scope to the instant tissues described within the specification

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPA 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The instant application fails to provide guidance to skilled artisans for generating any in vivo cell containing a first nucleic acid molecule with any promoter or enhancer operable for an encoding region of any protein involved in drug metabolism, encompassing those proteins that are not native to the cell. The instant claims read on an in vivo cell, natural organism, and transgenic organism for which the specification is not enabling. For example claim 46 specifically reads on a human and is not limited to an isolated human cell. The specification only teaches in vitro application of isolated cells for tissues, in particular liver tissues yet suggesting other tissues such as lung and kidney. As such, the specification is enabling for a recombinant cell that is isolated. While working examples are not, per se, required, the specification must provide adequate guidance such that one of skill in the art could practice the invention without undue experimentation. Given the lack of descriptive working examples in the

specification, and the unpredictability of genetically engineering cells for assays such as drug screening, the specification, as filed is enabling for the cells that are isolated and/or cultured (in vitro) cells, does not reasonably provide enablement for any cell (in vivo).

The following is a quotation of the **second** paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21-83 are vague and indefinite due to the lack of clarity of the promoter or enhancer encompassed by the claims. The metes and bounds of the parameters that define the promoter or enhancer are not clear. The promoter or enhancer is not required to be native to the protein of drug metabolism therefore, with the only requirement being the operable link, the promoter or enhancer can be any. Any non-novel protein has been done in the prior art thus unless there is an unexpected result, the method is a general screen for promoter activity, co-transfection. A differentiating factor could be that of a specific promoter sequence that has a sequence identifier as supported by Example I (p. 35); SEQ ID NO: 1 and 2 for the human PXR. Another differentiating factor could be that of a specific enhancer sequence that has a sequence identifier as seen again in Example I; SEQ ID NO: 3 and 4. This provides support for the PXR and CYP3A4 example. However, please note there is a lack of such specified sequences with sequence identifiers for the subsequent example, in which the generic method is performed with unspecified hAhR with the CYP1A1 gene. As such, the promoter or enhancer encompassed by the claims are indefinite.

Claims 21, 36-38 and 52 are vague and indefinite due to the lack of clarity of the phrase "proteins involved in drug metabolism" as seen for example in line 4. It is unclear as to the metes and bounds of the parameters that define drug metabolism and the encoded proteins that are to some undefined extent "involved" with drug metabolism. The protein involved drug metabolism is not required to be native to the cell, therefore can be any protein that in any manner or fashion affects drug metabolism. As such, the protein involved drug metabolism

encompassed by the claims are indefinite. Claims 22-51 and 53-83 are also indefinite due to dependency from claims 21 and 52.

Claims 21 and 52 are vague and indefinite due to the lack of clarity of the compound being referred to: in claim 21, lines 10 and 14; and in claim 52, lines 14 and 18. It is unclear if the first indicated compound that the "intracellular receptor or transcription factor is bound with, associated with or activated by" (claim 21, lines 9-10) is the same or different than that compound "that induces" (line 14). As such, claims 22-51 and 53-83 are also indefinite due to dependency from claims 21 and 52.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 21, 22, 29-34, 36-40, 42-45, 47, 48, 52-54, 61-66, 68-72, 74-77, 79 and 80 are rejected under 35 U.S.C. 102(b) as being anticipated by Honkakoski et al. (*Mol. Cell. Biol.*, Oct. 1998).

The instant claim 21 requires the following: a cell comprising:

- A first nucleic acid molecule comprising: a promoter or enhancer operable for a nucleic acid molecule encoding a protein involved in drug metabolism; and operable for a reporter gene
- A second nucleic acid molecule encoding an intracellular receptor or transcription factor that upon ligand (i.e. drugs) interaction will directly or

> indirectly activate the promoter and in turn the desired protein and reporter gene.

While the method is the use of the above cell in screening xenobiotic compounds for those that alter the desired protein's expression, thereby indicating some modification in drug metabolism.

Honkakoski et al. demonstrates a murine hepatocytic cell line (*claims 44, 45, 47, 48, 76, 77, 79, 80*) and an up-scalable method of screening xenobiotics for induced cytochrome P-450 protein expression as per the required limitations of the claims: endogenous enhancer (Phenobarbital-responsive enhancer module: PBREM) (*claims 21, 32, 34, 52, 64, 66*); CYP2B genes (*claims 22, 54*); transfected intracellular receptors CAR and retinoid X receptor (RXR) which upon ligand interaction bind to specific binding sites on the PBREM for activating the expression of the desired gene and PBREM linked reporter genes such as CAT reporter plasmid (p. 5652, 1st column, 2nd paragraph to p. 5653, 1st column, 3rd paragraph) and the betagalactosidase plasmid (figure 7) (*claims 29-33, 33, 36-38, 52, 53, 61-65*). The transfected receptors are indicated to be endogenously expressed (p. 5656, 1st column, lines 1-2) (*claims 42, 43, 74, 75*). The reference indicates that the orphan receptors (*claims 39, 71*) identified are suggested to "provide cells with the capability to induce the various CYP genes and other genes responsive to unlimited numbers of xenobiotic chemicals" (p. 5657, bridging paragraph between columns, last line). The reference also suggests that the intracellular receptors or transcription factors could be hormone receptors (p. 5657, 1st column, last paragraph) (*claims 40, 72*). The drug, chemical, and metabolite limitations of claims 36-38 and 68-70 are encompassed by the statement of the reference "[t]he CYP-dependent metabolism can [...] produce a practically unlimited number of potential ligands (both endogenous hormones and exogenous chemicals) for the nuclear receptors" (p. 5657, 1st column, last paragraph). Therefore Honkakoski et al. anticipates the instant claims.

Claims 21, 29, 31, 36, 41, 44-47, 52 and 53 are rejected under 35 U.S.C. 102(e) as being anticipated by Lohray et al. (USPN 6,054,453; filed 23 JAN 1998).

This rejection is maintained from the previous action mailed 20 June 2002, with respect to the previous claims 3, 4, 9, 11, 14-17, 19 and 20 for reasons of record and newly applied to the correlating claims 21, 29, 31, 36, 41, 44-47, 52 and 53. Applicants' argue that the GAL4 is not a protein involved in drug metabolism; however due to the lack clarity of the parameters of drug metabolism as recited above, the method of testing a compound and its determined "drug binding/activation capacity" (column 38, line 24) by operably linking a promoter with a reporter gene to determine a desired sequence's encoded activity is anticipated by the reference. Applicants' also argue that an intracellular receptor is not taught by the reference however, this is not a requirement of the claim in that either an intracellular receptor OR transcription factor can be encoded. As recited in the previous action, a transcriptional factor was demonstrated by the reference. Therefore the arguments are not persuasive to overcome the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-34, 36-40, 42-62, 64-66, 68-71, and 74-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honkakoski et al. (*Mol. Cell. Biol.*, Oct. 1998) as applied to claims 21, 22, 29-34, 36-40, 42-45, 47, 48, 52-54, 61-66, 68-72, 74-77, 79 and 80 above, in view of Iyer et al. (*Europ. J. Cancer*, 1998) and Windmill et al. (*Mutation Research*, 1997).

Honkakoski et al. does not teach the various other drug metabolizing enzymes of claims 23-28 and 55-60, nor the various tissues of claims 49-51 and 81-83.

Iyer et al. is a teaches the use of pharmacogenetics in screening drug toxicity that evaluate specific drug metabolizing enzymes (*claims 22-28, 54-60*) including glutathione S-thansferases, uridine diphosphate glucuronosyl-transferases, and cytochrome P450 enzymes (abstract, lines 5-8).

Windmill et al. demonstrates the expression of various drug metabolizing enzymes in a multitude of human organ systems (*claims 22-24, 27, 46, 49-51*). For example N-acetyltransferase "mRNA expression was detected in human liver, small intestine, colon, esophagus, bladder, ureter, stomach and lung"; "sulfotransferase expression in the human colon, small intestine, lung, stomach and liver" (abstract, lines 12-16); and a cytochrome P450 expression in "human liver, stomach, small and large intestine, gall bladder, appendix, lung, kidney and adrenals (p.156, 1st column, 1st paragraph).

Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to make the cell and perform the method of screening xenobiotics of Honkakoski et al and further modify the protein involved in drug metabolism to include other proteins that contribute to drug metabolism such as in chemoresistance such as glucuronosyl transferases, N-acetyltransgerases, p-glyoproteins, gluthathione transgerases and sulfotransferases as per the teachings of Iyer et al. Thus, one of ordinary skill in the art would have been motivated to do the modifications taught by Iyer et al. in the instant generic cell and screening method due to the advantages of studying expression of the instant drug metabolizing enzymes play a key role in cancer therapy and are involved in attributing to failed cancer treatments. In addition, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to further modify the cells to included those of an isolate human cell line and or various systems other than the liver (lung, gastrointestinal tract and kidney) as per the teachings of Windmill et al. Thus, one of ordinary skill in the art would have been motivated to do the modifications taught by Windmill et al. in the instant generic cell and screening method due to these drug metabolizing enzymes are not limited to one organ system: for example N-acetyltransferase "mRNA expression was detected in human liver, small intestine, colon,

esophagus, bladder, ureter, stomach and lung" and "sulfotransferase expression in the human colon, small intestine, lung, stomach and liver" (abstract, lines 12-16).

Claims 22, 32-35, 39, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lohray et al. (USPN 6,054,453) as applied to claim 21 above in view of Luskey et al (USPN 6,262,118; claim 22), Foulkes et al (USPN 5,976,793; claims 32-34), Boeke et al (USPN 5,840,579; claim 35), Klein et al (USPN 6,255,959; claim 39) and Sherr et al (USPN 6,303,772; claims 42 and 43).

This rejection is maintained from the previous action mailed 20 June 2002, with respect to the previous claims 2, 5-8, 10, 12 and 13 for reasons of record and newly applied to the correlating claims 22, 32-35, 39, 42 and 43. As described above, Lohray et al demonstrates claim 21 as applied above due to the lack clarity of the parameters of drug metabolism as recited above, the method of testing a compound and its determined "drug binding/activation capacity" (column 38, line 24) by operably linking a promoter with a reporter gene to determine a desired sequence's encoded activity is demonstrated by Lohray et al. With regard to applicant's argument that the secondary references do not perform the following:

> "teach or suggest a cell comprising a first nucleic acid molecule comprising a promoter or enhancer operable for a nucleic acid molecule encoding a protein involved in drug metabolism operably linked to a reporter gene, and a second nucleic acid molecule encoding an intracellular receptor or a transcription factor, which when bound with, associated with or activated by a compound, con operably bind with, associate with, or activate the promorter or enhancer resulting in the expression of the reporter gene",

the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Thus the rejections are reiterated and maintained from the previous office action.

Information Disclosure Statement

The information disclosure statement filed 21 October 2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that

portion which caused it to be listed; and all other information or that portion which caused it to be listed. The US Patent with document number 20020022599 of Synold et al was not provided; in addition, the information provided on the document appears to be incorrect. Therefore this listed reference was not considered.

Conclusion

Claims 21-51 are rejected under 35 U.S.C. 101.

Claims 21-83 are rejected under 35 U.S.C. 112, first paragraph.

Claims 21-83 are rejected under 35 U.S.C. 112, second paragraph.

Claims 21, 22, 29-34, 36-40, 42-45, 47, 48, 52-54, 61-66, 68-72, 74-77, 79 and 80 are rejected under 35 U.S.C. 102(b) as being anticipated by Honkakoski et al. (*Mol. Cell. Biol.*, Oct. 1998).

Claims 21, 29, 31, 36, 41, 44-47, 52 and 53 are rejected under 35 U.S.C. 102(e) as being anticipated by Lohray et al. (USPN 6,054,453; filed 23 Jan 1998).

Claims 21-34, 36-40, 42-62, 64-66, 68-71, and 74-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honkakoski et al. (*Mol. Cell. Biol.*, Oct. 1998), in view of Iyer et al. (*Europ. J. Cancer*, 1998) and Windmill et al. (*Mutation Research*, 1997).

Claims 22, 32-35, 39, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lohray et al. (USPN 6,054,453), in view of Luskey et al (USPN 6,262,118), Foulkes et al (USPN 5,976,793), Boeke et al (USPN 5,840,579), Klein et al (USPN 6,255,959) and Sherr et al (USPN 6,303,772).

No claim is allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Monika B. Sheinberg, whose telephone number is (703) 306-0511. The examiner can normally be reached on Monday-Friday from 9 A.M to 5 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

May 22, 2003

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